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Arylsulfatase A Pseudodeficiency-Associated Mutations: Population Studies and Identification of a Novel Haplotype

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Pseudodeficiency of arylsulfatase A is characterized by reduction of arylsulfatase A activity without neurodegeneration, making it an important complication when diagnosing metachromatic leukodystrophy. Two DNA substitutions are associated with arylsulfatase A pseudodeficiency. One, 1788A→G, results in the loss of an *N*-glycosylated asparagine in the protein, and the second, 2723A→G, removes the polyadenylation signal site of the mRNA. Previously, the polyadenylation signal site variant was observed only in the presence of the *N*-glycosylation site variant, although the latter has been reported to occur in the absence of the polyadenylation signal site variant. We investigated the frequencies of these alleles and their linkage disequilibrium in a number of populations and in psychiatric patients. While the *N*-glycosylation site variant had a high frequency in the Bantu-speaking people from Southern Africa (0.44), the San of Southern Africa (0.22), African Americans (0.37), and Cheyenne Indians (0.375), the polyadenylation signal site variant was absent in these groups. The mutated polyadenylation signal site was found only in the Caucasian groups surveyed. Two Caucasian sibs were identified with the pseudodeficiency polyadenylation signal site variant in the absence of the *N*-glycosylation site variant, indicating that linkage disequilibrium between the two polymorphisms is not perfect.

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INTRODUCTION

Sulfatide is a membrane sphingolipid found in relatively high concentrations in brain tissue [Vos et al., 1994]. Arylsulfatase A (ARSA), a lysosomal enzyme, catalyzes the removal of the sulfate group from sulfatide to form galactocerebroside. A deficiency of ARSA activity results in the accumulation of sulfatide and, in humans, the neurodegenerative disorder metachromatic leukodystrophy (MLD) [Kolodny and Fluharty, 1995]. The ARSA gene (*ARSA*) is located on chromosome 22q, and a number of mutations of *ARSA* have been identified which cause MLD [reviewed in Gieselmann et al., 1994; Barth et al., 1994a].

Pseudodeficiency of ARSA is characterized by reduced levels of ARSA activity, but a normal clinical phenotype. The activity of ARSA in pseudodeficient individuals is typically about 15% of normal when determined with the artificial substrate p-nitrocatechol-sulfate [Chang and Davidson, 1983; Chang et al., 1984]. Although it does not lead to neurodegenerative disease, ARSA pseudodeficiency is a complicating factor in the diagnosis of MLD and MLD carrier status in families possessing the pseudodeficiency allele [Francis et al., 1993; Shen et al., 1993]. Two mutations in the ARSA gene are associated with pseudodeficiency. These are an A to G transition at nucleotide 1788 of the genomic sequence, which substitutes serine for asparagine at amino acid 350, resulting in the loss of an *N*-glycosylation site of the ARSA protein, and an A to G transition at nucleotide 2723, resulting in the loss of the polyadenylation signal site [Gieselmann et al., 1989]. Both of these mutations contribute to a reduction in ARSA enzymic activity. The 2723A→G mutation leads to the loss of the normal 2.1-kilobase mRNA for ARSA. Deficiency of this mRNA species is thought to result in diminished synthesis of ARSA [Gieselmann et al., 1989]. The 1788A→G mutation has also been found to lead to a reduction in ARSA enzymic activity [Shen et al., 1993; Park et al.,

1996]. The loss of the *N*-glycosylation site by this mutation leads to an increased intracellular turnover rate for the ARSA protein [Park et al., 1996]. While the *N*-glycosylation site mutation has been found without the polyadenylation signal site mutation on the same allele, the latter has thus far only been reported in association with the *N*-glycosylation site mutation.

MLD affects persons in many regions of the world. The diagnosis of MLD or determination of MLD carrier status by assay of ARSA activity is complicated in the presence of the pseudodeficiency alleles. Therefore, it is important to know the occurrence of ARSA pseudodeficiency in different populations. Here, we describe the frequency of pseudodeficiency-associated mutations in selected populations and the existence of the polyadenylation signal site mutation in an ARSA gene without the *N*-glycosylation site mutation.

MATERIALS AND METHODS

DNA samples were obtained from the following groups: 24 Cheyenne Indians, 67 United States Caucasians, 19 African Americans, 24 Southern African Bantu speakers, 23 Southern African San, and 100 subjects from Finland. All subjects were unrelated adults. Of the 67 United States Caucasians, 28 were normal controls and 39 were psychiatric patients. Of the latter group, 31 were alcoholic (9 with symptoms of depression, 2 with phobic disorder, and 6 with both), 3 had only depression, 1 had phobic disorder, and 4 had both depression and phobic disorder. Some of the Cheyenne and Finnish subjects have been referred to previously [Goldman et al., 1992, 1993]. Of the 100 Finnish DNA samples, 50 were from persons free of alcohol abuse, substance abuse, or major mental illness, and 50 were from alcoholics, many of whom were violent offenders. Approval for this project was obtained from the Institutional Review Board (IRB) of University of Medicine and Dentistry of New Jersey-Robert-Wood Johnson Medical School.

The two pseudodeficiency mutations of ARSA were detected by PCR amplification and digestion with *Mae*III and *Bsr*I restriction endonucleases as described [Ricketts et al., 1995], or by dot-hybridization of PCR-amplified DNA with allele-specific oligonucleotides [Gieselmann et al., 1989]. The dot-hybridization analysis was modified for digoxygenin-labeled probes (Genius system, Boehringer-Mannheim, Indianapolis, IN), and the fluorescent signals were detected and quantified using a GS250 Phosphorimager (Biorad Laboratories, Hercules, CA). For DNA sequencing, the fragment of the ARSA gene from nucleotides 1672–2816 was amplified using oligonucleotides ASA7c (5′-TTGATGGCGAACTGAGTGAC) and ASA8nc (5′-TTCCTCATTCGTACCACAGG) synthesized by National Biosciences, Plymouth, MN. The amplified product was cloned into the TA vector (Invitrogen, San Diego, CA). Clones with the polyadenylation signal site mutation were identified by digestion of plasmid DNA with *Mae*III and sequenced using the chain termination method. The phase of the *Bgl*I polymorphic site was determined by PCR amplification of genomic DNA with oligonucleotides ASA13c and ASA16nc, and by restriction digestion with *Bgl*I, as described [Ricketts et al., 1996].

Allele frequencies were compared using a two-tailed Fisher's exact test, and linkage disequilibrium was calculated as described by Weir [1990].

RESULTS

Frequency of Pseudodeficiency Mutations

Pseudodeficiency of ARSA is due to two A to G transitions: 1788G removes one of the three potential *N*-glycosylation sites, and 2723G removes the polyadenylation signal site. We refer to the pseudodeficiency haplotypes as 1788G-2723A (mutation only at the *N*-glycosylation site), 1788G-2723G (mutation at both the pseudodeficiency sites), and 1788A-2723G (mutation only at the polyadenylation signal site). The frequencies of the four ARSA haplotypes involving the pseudodeficiency mutation sites were determined in a number of populations and in psychiatric patients. The frequency of the pseudodeficiency *N*-glycosylation mutation did not differ significantly between psychiatric patients and normal controls: United States Caucasians, 0.21 (17/78) and 0.23 (13/56), respectively, $P = 0.837$; Finnish Caucasians, 0.05 (5/100) and 0.07 (7/100), respectively, $P = 0.767$. Similarly, the frequency of the pseudodeficiency polyadenylation signal site mutation did not differ significantly between psychiatric patients and normal controls: United States Caucasians, 0.13 (10/78) and 0.09 (5/56), respectively, $P = 0.584$; Finnish Caucasians, 0.03 (3/100) and 0.04 (4/100), respectively, $P = 1.00$. Therefore, data from patient and control populations were pooled for analyses of frequency and disequilibrium of pseudodeficiency mutations (Table I).

There was a large variation in frequencies of the ARSA pseudodeficiency alleles between the populations we investigated. The polyadenylation signal site mutation (2723G) was found only among the Caucasian groups. Interestingly, this allele was found at a very low frequency in the Finnish population as compared to North American Caucasians and other European, Middle Eastern, and Australian populations (Table II). The highest frequency of the N-glycosylation site pseudodeficiency mutation (1788G) was observed in the Bantu-speaking people of Southern Africa. As in the African American, San, and Cheyenne Indian population samples, the polyadenylation signal site mutation was absent in the Southern African populations sampled. This suggests that the polyadenylation signal site mutation originated in the Caucasian population, possibly as a single event in an ARSA gene with a pre-existing *N*-glycosylation site mutation. The linkage disequilibrium, D, between the two pseudodeficiency mutations in the U.S. Caucasian population was 0.0079 ± 0.017, indicating significant disequilibrium between the two mutations. Normalizing D by the maximum value that it can obtain for the observed frequencies gives $D' = 0.914$ [Weir, 1990]. While this value is very high, it is not absolute, because of a novel 1788A-2723G haplotype in one subject.

A Novel Pseudodeficiency Haplotype

In previous surveys, the polyadenylation signal site mutation has never been reported in the absence of the *N*-glycosylation site mutation [Barth et al., 1994b; Zloto-

TABLE I. Occurrence of ARSA Pseudodeficiency Mutations in Different Populations*

Population	No. of subjects	Frequency of pseudodeficiency haplotypes			Frequency of pseudodeficiency mutations	
		1788G-2723A	1788G-2723G[a]	1788A-2723G	1788G	2723G
U.S. Caucasians	67	0.119 (0.028)	0.104 (0.026)	0.0075	0.224 (0.036)	0.112 (0.027)
Finnish Caucasians	100	0.025 (0.011)	0.035 (0.013)	0	0.060 (0.017)	0.035 (0.013)
Cheyenne Indians	24	0.375 (0.070)	0	0	0.375 (0.070)	0
African Americans	19	0.370 (0.078)	0	0	0.370 (0.078)	0
S. African Bantu	24	0.440 (0.072)	0	0	0.440 (0.072)	0
S. African San	23	0.220 (0.061)	0	0	0.220 (0.061)	0

*Standard errors for frequencies are presented in parentheses below frequencies where this calculation is meaningful.
[a]Assumes that individuals heterozygous at both pseudodeficiency sites have the A→G transitions at the two pseudodeficiency sites on the same gene.

gora et al., 1994; Nelson et al., 1991; Chabas et al., 1993; Ott et al., 1994]. One Caucasian subject in this study was found to be heterozygous for the polyadenylation signal site mutation, but homozygous-normal at the *N*-glycosylation site by PCR amplification and restriction endonuclease digestion. A sibling of the patient had the same ARSA haplotypes. In order to establish that this finding did not reflect another mutation influencing the restriction enzymes used, a region of the ARSA gene harboring both pseudodeficiency sites from these subjects was amplified by PCR and cloned. Isolated ARSA clones with the polyadenylation signal site mutation were identified by digestion with *Mae*III, and the DNA was sequenced (Fig. 1). The sequence analysis confirmed that the cloned genes had the A to G transition at nucleotide 2723, but were normal at the *N*-glycosylation site (1788A). With the exception of previously-known polymorphic sites, no other mutations were found in the DNA clones sequenced. By sequencing across both pseudodeficiency sites in clones from the subject and his sibling, we confirmed the existence of a novel ARSA pseudodeficiency haplotype with only the polyadenylation signal site mutation. Zlotogora et al. [1994] did not find this haplotype among 660 ARSA alleles screened, a finding indicative of the rarity of this novel allele. Even though apparently very rare, the existence of this novel haplotype should be considered when the possibility of ARSA pseudodeficiency is being investigated in families at risk for MLD.

It has been reported that the 1788G-2723G pseudodeficiency gene of ARSA is associated with a unique haplotype [Zlotogora et al., 1994]. This haplotype is defined

TABLE II. Summary of Previously Reported Data on the Frequency of ARSA Pseudodeficiency Mutations in Different Populations*

Population	No. of subjects	Frequency of pseudodeficiency haplotypes (%)			Frequency of pseudodeficiency mutations (%)	
		1788G-2723A	1788G-2723G	1788A-2723G	1788G	2723G
Australian[a]	73	4.8	9.6	0	14.4	9.6
United Kingdom[b]	154	5.2	12.3	0	17.5	12.3
Ashkenazi Jews[c]	92	0.6	13.3	0	13.9	13.3
Non-Ashkenazi Jews[c]	51	3.6	12.2	0	15.8	12.2
Yemenites[c]	150	3.5	22.7	0	26.2	22.7
Arabs[c]	61	6.8	9.2	0	16.0	9.2
Spanish[d]	55	nd	nd	nd	nd	12.7
East Indian[e]	100	1	12.5	0	13.5	12.5
Oriental[e]	100	21	0.5	0	21.5	0.5
Blacks[e]	100	32	0.5	0	32.5	0.5
Caucasians[e]	100	6	7.5	0	13.5	7.5

* nd, not determined.
[a] Nelson et al., 1991.
[b] Barth et al., 1994b.
[c] Zlotogora et al., 1994 (Israeli study).
[d] Chabas et al., 1993.
[e] Ott et al., 1994 (Canadian study).

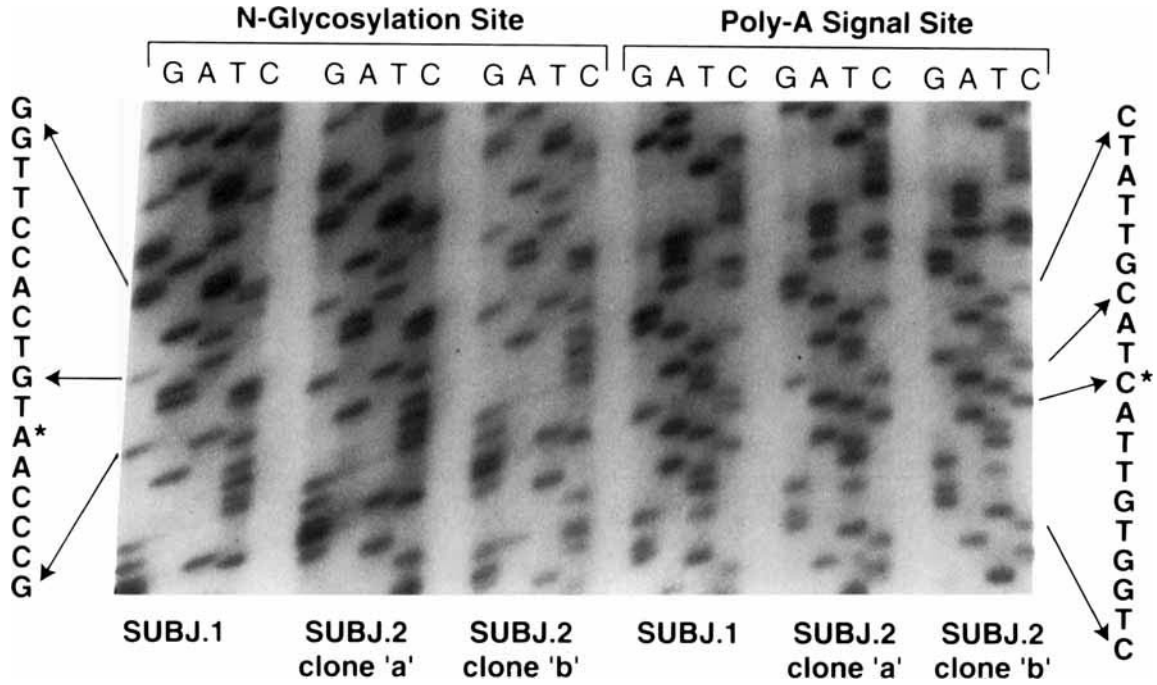

Fig. 1. Autoradiograph of DNA sequence analysis of ARSA genomic clones from individuals with only the polyadenylation signal site pseudodeficiency mutation. One clone from subject 2 and two clones from subject 1 were each sequenced across both the polyadenylation signal site and the *N*-glycosylation pseudodeficiency site of arylsulfatase A. While the codon for asparagine (AAT) is normal at the *N*-glycosylation site of all the clones, the polyadenylation signal site has the pseudodeficiency mutation (ATCATTG instead of ATTATTG). The nucleotides marked with an asterisk represent those mutated in the pseudodeficiency alleles.

by polymorphisms affecting sites for restriction enzymes *Bgl*I, *Bsr*I and *BamH*I in the ARSA gene. The *Bgl*I polymorphism arises from a G to C transversion at nucleotide 842, changing the encoded tryptophan at amino acid residue 193 to cysteine [Polten et al., 1991; Ricketts et al., 1996]. The *Bsr*I site polymorphism at nucleotide 2161 effects a serine-to-threonine change at amino acid residue 391, and the *BamH*I polymorphic site at nucleotide 2213 is located within intron 7 of the ARSA gene [Polten et al., 1991]. The haplotype associated with the presence of both pseudodeficiency mutations (1788G-2723G) is *Bgl*I(+), and *BamH*I(−), where (+) indicates cutting by the restriction enzyme at the site [Zlotogora et al., 1994]. However, a Canadian study found the *Bsr*I polymorphism in all haplotypes [Ott et al., 1994]. This indicates that the unique haplotype associated with the 1788G-2723G ARSA gene in the Israeli study [Zlotogora et al., 1994] may not describe the situation in all populations.

In order to investigate the origin of the gene with the novel pseudodeficiency haplotype found in our 2 subjects, the phase of these polymorphic sites was determined. The phase of the *Bsr*I and *BamH*I sites was determined directly from the DNA sequence of the cloned ARSA gene fragment with the polyadenylation signal site mutation, while that of the *Bgl*I site was determined by PCR-amplification and restriction enzyme digestion, as described in Materials and Methods. The 1788A-2723G cloned ARSA genes were found to be *Bgl*I(+), *Bsr*I(−), and *BamH*I(−). The phase of the *Bsr*I site, therefore, is different in the 1788A-2723G gene than that found in the 1788G-2723G ARSA pseudodeficiency genes of 31 homozygous individuals [Zlotogora et al., 1994]. The different phase of the *Bsr*I polymorphic site, which is only 373 nucleotides from the *N*-glycosylation site at nucleotide 1788 in the ARSA gene, suggests that the 1788A-2723G ARSA gene did not originate by reversion of a mutated *N*-glycosylation site. The polyadenylation signal site mutation may therefore have occurred as a de novo mutation on a gene without the *N*-glycosylation site mutation, or may have arisen from a recombination event between a normal gene and a 1788G-2723G pseudodeficiency gene. The latter hypothesis is considered more likely to account for the origin of this novel 1788A-2723G ARSA gene. The ARSA gene between nucleotides 2161–2723, where recombination may have occurred, includes 32 nucleotides of exon 7, the 115-nucleotide intron 7, the 320-nucleotide exon 8, and 94 nucleotides of untranslated sequence preceding the polyadenylation signal site. There was no deviation from the known sequence in this region of the ARSA gene with the novel pseudodeficiency haplotype.

DISCUSSION

Because measurement of ARSA activity is one of the most frequently performed lysosomal enzyme tests, the presence of pseudodeficiency mutations in a significant proportion of the population is important in the diagnosis of MLD [Francis et al., 1993; Wenger and Louie,

1991]. MLD occurs in forms ranging from late-infantile to adult-onset, with age of onset largely determined by the amount of residual ARSA enzymic activity [Polten et al., 1991]. While reduced levels of ARSA enzymic activity in pseudodeficiency do not cause disease, ARSA activity in persons with adult-onset metachromatic leukodystrophy and persons homozygous for the pseudodeficiency mutations can be very similar [Hageman et al., 1995; Kolodny and Fluharty, 1995]. Persons with one MLD and one pseudodeficient ARSA gene have very low platelet ARSA activity but are free of neurological disease [Wenger and Louie, 1991; Penzien et al., 1993]. In addition to DNA analyses, the metabolism of radioactively-labeled sulfatide in cultured fibroblast cells from patients can also be used to help distinguish MLD from ARSA pseudodeficiency [Wenger and Louie, 1991]. This is important because the presence of pseudodeficiency mutations does not negate the possibility of an MLD mutation on the same ARSA gene [Gieselmann et al., 1991; Zlotogora et al., 1995].

In this study, we investigated the frequency of both of the pseudodeficiency mutations in several ethnic groups and in psychiatric patients. The polyadenylation signal site mutation of ARSA was found only in Caucasian subjects and not in Cheyenne Indians, African Americans, or Southern African San and Southern African Bantu-speaking Negroid persons. Previous published reports, with the exception of an abstract [Ott et al., 1994], have been largely restricted to the analysis of pseudodeficiency mutations in Caucasian subjects [Barth et al., 1994b; Zlotogora et al., 1994; Nelson et al., 1991; Chabas et al., 1993]. In agreement with our findings, Ott et al. [1994] found the polyadenylation signal site mutation to be extremely rare in Black and Oriental subjects (0.5% of alleles investigated). However, the existence of 1788G-2723G ARSA pseudodeficiency genes should not be discounted in these groups, as they have been found in non-Caucasians [Ott et al., 1994].

In the course of this investigation, one Caucasian subject and his sibling were identified as being heterozygous for an ARSA gene with the polyadenylation signal site mutation (but without the *N*-glycosylation site mutation) and a normal ARSA gene. This 1788A-2723G ARSA gene has not previously been found, but may have been missed in individuals who are compound heterozygotes with 1788G-2723A and 1788A-2723G ARSA genes. Such individuals could be confused with persons heterozygous for a normal (1788A-2723A) and a 1788G-2723G pseudodeficiency ARSA gene. Homozygosity for the 1788A-2723G ARSA gene may be very rare, and it is not certain how much the activity of ARSA will be reduced in homozygous individuals. Nonetheless, this gene does exist as one of the three possible combinations of pseudodeficiency-associated mutations. The identification and measurement of ARSA activity in 1788A-2723G homozygotes or in 1788G-2723G/1788A-2723G compound heterozygotes, will enable determination of the influence of the 1788A-2723G gene on ARSA enzymic activity. This will be necessary before any firm conclusions concerning the influence of the 1788A-2723G gene on ARSA enzymic activity can be made.

Both the subject and his sister with the 1788A-2723G haplotype were psychiatric patients with depressive and phobic disorder. The association of psychiatric disorders with this haplotype of ARSA is most likely coincidental. Identification of additional persons with the polyadenylation signal site mutation in the absence of the *N*-glycosylation site pseudodeficiency mutation of ARSA will serve to clarify this. The manifestation of early psychiatric problems prior to onset of MLD in adult patients gave rise to the hypothesis that reduced ARSA activity without MLD may predispose persons to psychiatric disorders [Shah et al., 1985; Propping et al., 1986; Hohenschutz et al., 1988, 1989; Penzien et al., 1993; Park et al., 1996]. We found large variations in the frequencies of pseudodeficiency mutations, e.g., the rates in the Finnish Caucasian population were very different from those in the U.S. Caucasian, Cheyenne Indian, or African populations. The large variation in frequencies of pseudodeficiency mutations between populations indicates that association studies to test the above hypothesis need to be carried out in ethnically matched groups and interpreted with care.

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REFERENCES

Barth ML, Fenson A, Harris A (1994a): The arylsulfatase A gene and molecular genetics of metachromatic leukodystrophy. J Med Genet 31:663–666.

Barth ML, Ward C, Harris A, Saad A, Fensom A (1994b): Frequency of arylsulfatase A pseudodeficiency associated mutations in a healthy population. J Med Genet 31:667–671.

Chabas A, Castellvi S, Bayes M, Balcells S, Grinberg D, Vilageliu LI, Marfany G, Lissens W, Gonzalez-Duarte R (1993): Frequency of the arylsulfatase A pseudodeficiency allele in the Spanish population. Clin Genet 44:320–323.

Chang PL, Davidson RG (1983): Pseudo arylsulfatase A deficiency in healthy individuals: Genetic and biochemical relationship to metachromatic leukodystrophy. Proc Natl Acad Sci USA 80:7323–7327.

Chang PL, Rosa NE, Varey PA, Kihara H, Kolodny EH, Davidson RG (1984): Diagnosis of pseudo-arylsulfatase A deficiency with electrophoretic techniques. Pediatr Res 18:1042–1045.

Francis GS, Bonni A, Shen N, Hechtman P, Yamut B, Carpenter S, Karpati G, Chang PL (1993): Metachromatic leukodystrophy: Multiple nonfunctional and pseudodeficiency alleles in a pedigree: Problems with diagnosis and counseling. Ann Neurol 34:212–218.

Gieselmann V, Polten A, Kreysing J, von Figura K (1989): Arylsulfatase A pseudodeficiency: Loss of a polyadenylation signal and *N*-glycosylation site. Proc Natl Acad Sci USA 86:9436–9440.

Gieselmann V, Fluharty AL, Tønnesen T, von Figura K (1991): Mutations in the arylsulfatase A pseudodeficiency allele causing metachromatic leukodystrophy. Am J Hum Genet 49:407–413.

Gieselmann V, Polten A, Kreysing K, von Figura K (1994): Molecular genetics of metachromatic leukodystrophy. J Inherited Metab Dis 17:500–509.

Goldman D, Dean M, Brown GL, Bolos AM, Tokola R, Virkkunen M, Linnoila M (1992): D2 dopamine receptor genotype and cerebrospinal fluid homovanillic acid, 5-hydroxyindoleacetic acid and 3-methoxy-4-hydroxyphenylglycol in alcoholics in Finland and the United States. Acta Psychiatr Scand 86:351–357.

Goldman D, Brown GL, Albaugh B, Robin R, Goodson S, Trunzo M, Akhtar L, Lucas-Derse S, Long J, Linnoila M, Dean M (1993): DRD2 dopamine receptor genotype, linkage disequilibrium, and alcoholism in American Indians and other populations. Alcohol Clin Exp Res 17:199–204.

Hageman ATM, Gabreëls FJM, de Jong JGN, Gabreëls-Festen AAWM, van den Berg CJMG, van Oost BA, Wevers RA (1995): Clinical symptoms of adult metachromatic leukodystrophy and arylsulfatase A pseudodeficiency. Arch Neurol 52:408–413.

Hohenschutz C, Friedl W, Schlör K-H, Waheed A, Conzelmann E, Sandhoff K, Propping P (1988): Probable metachromatic leukodystrophy/pseudodeficiency compound heterozygote at the arylsulfatase A locus with neurological and psychiatric symptomatology. Am J Med Genet 31:161–175.

Hohenschutz C, Eich P, Friedl W, Waheed A, Conzelmann E, Propping P (1989): Pseudodeficiency of arylsulfatase A: A common genetic polymorphism with possible disease implications. Hum Genet 82: 45–48.

Kolodny EH, Fluharty AL (1995): Metachromatic leukodystrophy and multiple sulfatase deficiency: Sulfatide lipidosis. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds): "The Metabolic and Molecular Bases of Inherited Disease." New York: McGraw Hill, pp 2693–2739.

Nelson PV, Carey WF, Morris CP (1991): Population frequency of the arylsulfatase A pseudo-deficiency allele. Hum Genet 87:87–88.

Ott AR, Waye JS, Chang PL (1994): Evolutionary relationship and ethnic variations of two tightly linked mutations in the gene coding for the lysosomal enzyme arylsulfatase A. Am J Hum Genet 55:160.

Park DS, Poretz RD, Stein S, Nora R, Manowitz P (1996): The association of alcoholism with the *N*-glycosylation polymorphism of pseudodeficient human arylsulfatase A. Alcohol Clin Exp Res 20: 228–233.

Penzien JM, Kappler J, Herschkowitz N, Schuknecht B, Leinekugel P, Propping P, Tønnesen T, Lou H, Moser H, Zierz S, Conzelmann E, Gieselmann V (1993): Compound heterozygosity for metachromatic leukodystrophy and arylsulfatase A pseudodeficiency alleles is not associated with progressive neurological disease. Am J Hum Genet 52:557–564.

Polten A, Fluharty AL, Fluharty CB, Kappler J, von Figura K, Gieselmann V (1991): Molecular basis of different forms of metachromatic leukodystrophy. N Engl J Med 324:18–22.

Propping P, Friedl W, Huschka M, Schlör K-H, Reimer F, Lee-Vaupel M, Conzelmann E, Sandhoff K (1986): The influence of low arylsulfatase A activity on neuropsychiatric morbidity: A large-scale screening in patients. Hum Genet 74:244–248.

Ricketts MH, Zhang X, Manowitz P (1995): A method for rapid detection of arylsulfatase A pseudodeficiency mutations. Hum Hered 45:235–240.

Ricketts MH, Amsterdam JD, Park DS, Yang R, Poretz RD, Zhang X, Fanalle M, Baddoo A, Manowitz P (1996): A novel arylsulfatase A protein variant and genotype in two patients with major depression. J Affect Disord (in press).

Shah NS, Johnson RC, Stone RK, Mahon-Haft H (1985): Prevalence of partial cerebroside sulfate sulfatase (arylsulfatase A) defect in adult psychiatric patients. Biol Psychiatry 20:50–57.

Shen N, Li Z-G, Waye JS, Francis G, Chang PL (1993): Complications in the genotypic molecular diagnosis of pseudo arylsulfatase A deficiency. Am J Med Genet 45:631–637.

Vos JP, Lopes-Cardozo M, Gadella BM (1994): Metabolic and functional aspects of sulfogalactolipids. Biochim Biophys Acta 1211: 125–149.

Weir BS (1990): "Genetic Data Analysis: Methods for Discrete Population Genetic Data." Sunderland, MA: Sinauer Associates, pp 89–93.

Wenger DA, Louie E (1991): Pseudodeficiencies of arylsulfatase A and galactocerebrosidase activities. Dev Neurosci 13:216–221.

Zlotogora J, Furman-Shaharabani Y, Goldenfum S, Winchester B, von Figura K, Gieselmann V (1994): Arylsulfatase A pseudodeficiency: A common polymorphism which is associated with a unique haplotype. Am J Med Genet 562:146–150.

Zlotogora J, Bach G, Bösenberg C, Barak Y, von Figura K, Gieselmann V (1995): Molecular basis of late infantile metachromatic leukodystrophy in the Habbanite Jews. Hum Mutat 5:137–143.